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Insulin resistance as a predictor of cardiovascular morbidity and end-stage renal disease

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ABSTRACT

Background: Cardiovascular disease (CVD) is the main risk factor of morbidity and mortality in chronic kidney disease (CKD) patients. Insulin resistance (IR) has been reported to be a strong risk factor for CVD. The purpose of this study was to examine the usefulness of IR as a predictor of cardiovascular morbidity and end-stage renal disease (ESRD).
Methods: We followed during a period of 56 months 119 type 2 diabetic CKD patients (stages 2 to 4) without history of CVD at the beginning of the study. Several laboratory parameters and left ventricular mass index (LVMI) were analyzed. The degree of IR was estimated by the Homeostasis Model Assessment (HOMA-IR). Cardiovascular morbidity was assessed according to the presence of cardiovascular hospital admission during the study period, defined by admissions caused by coronary heart disease, congestive heart failure, peripheral vascular disease and cerebrovascular disease. The population was divided in two groups: G-1 with cardiovascular admission ($n = 48$) and G-2: without admission ($n = 71$). The multiple logistic regression was used to assess predictors of cardiovascular morbidity and ESRD. The renal survival was evaluated by the Kaplan–Meier and long-rank test.
Results: We found that G-1 patients showed significantly higher HOMA-IR (3.8 vs 0.77, $p = 0.0001$) and that HOMA-IR upper tercile showed significantly higher age, eGFR, LVMI, phosphorus, iPTH and IL-6. In a multivariate logistic regression model HOMA-IR and IL-6 were independent risk factors of cardiovascular morbidity (OR = 2.847 [95% CI 1.048–7.735, $p = 0.012$] and OR = 2.483 [95% CI 1.221–5.049, $p = 0.04$], respectively). In a univariate logistic regression model patients in the upper tercile presented significantly more cardiovascular admissions that in the lower tercile. CKD progression to ESRD was observed in 24 patients and those in the upper HOMA-IR tercile showed a higher CKD progression to ESRD than the rest of study patients. A multivariate logistic regression model showed that HOMA-IR (OR = 1.034, 95% CI 1.065–1.650, $p = 0.040$) was an independent predictor of ESRD. Kaplan–Meier analysis showed a difference in renal survival in the HOMA-IR terciles (log rank = 8.093; $p = 0.017$).
Conclusion: In our study IR is an important risk factor for cardiovascular morbidity and ESRD in a diabetic CKD population.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in chronic kidney disease (CKD) patients with a higher incidence than in general population, even after adjusting for age and diabetic status (Caravaca, Cerezo, Macías, et al., 2010; Fragoso, Silva, Gundlach, et al., 2014; Liao, Sung, Hung, et al., 2012; Moehlecke, Leitão, Kramer, et al., 2010). This increased cardiovascular morbidity and mortality progressively increases with the decline of the glomerular filtration rate (GFR) (Fragoso et al., 2014) and cannot be explained only by traditional risk factors (Liao et al., 2012). Non-traditional risk factors like insulin resistance (IR), among others, have a critical role in this adverse outcome (Fragoso et al., 2014). Identifying risk factors may be the best approach do prevent and delay adverse outcomes (Liao et al., 2012).

IR is characterized by a functional deficit in insulin despite high plasma levels which leads to several changes in the composition of plasma lipids, coagulation, endothelial function, vascular resistance and endocrine changes that in combination has been shown to be associated to increased CVD risk in the general population (Caravaca et al., 2010). IR is a common metabolic disorder in patients with mild-to-moderate CKD disease, but the role that IR plays in the development of CVD in the CKD population has not been subject of many studies (Caravaca et al., 2010; Liao et al., 2012).

Conflict of interest statement: None declared.

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In our study we used the homeostatic model assessment (HOMA-IR) that estimates IR from fasting plasma glucose and insulin concentration (Barr, Cameron, Balkau, et al., 2010; Liao et al., 2012). This is a reliable surrogate marker of IR (An, Yu, Zhang, et al., 2012; Becker, Kronenberg, & Kielstein, 2005; Bonora, Formentini, Calcaterra, et al., 2002; Bonora, Kiechl, Willeit, et al., 2007; Dinh, Lankisch, Nickl, et al., 2010; Resnick, Jones, & Ruotolo, 2003; Sciacqua, Marini, Hribal, et al., 2013; Shinohara, Shoji, Emoto, et al., 2002) widely used in clinical studies (Barr et al., 2010; Becker et al., 2005; Liao et al., 2012) both in nondiabetic and diabetic subjects (Bonora et al., 2002) and also in patients with renal failure (Liao et al., 2012; Shinohara et al., 2002).

The study aims to determine whether IR is associated with the development of new cardiovascular events and CKD progression to end-stage renal disease (ESRD) in a population of type 2 diabetic patients with nephropathy.

2. Subjects, materials and methods

2.1. Study population

We followed in our outpatient diabetic nephropathy clinic, during a period of 56 months, 119 type 2 diabetic patients in stages 2, 3 and 4 of CKD without history of CVD (see below) and in a stable clinical condition, with no acute intercurrent disease at the beginning of the study. The exclusion criteria were: previous CVD—defined as a history of one or more of the following: non-fatal myocardial infarction, angina pectoris (stable or unstable), stroke or transient ischemic attacks, peripheral vascular disease or congestive heart failure; uncontrolled hypertension (BP ≥ 140/90 mm Hg), type 1 diabetes, non-diabetic renal disease, neoplastic or infectious diseases. All hospital admissions not caused by cardiovascular events were excluded.

The classification of diabetes was performed based on the guidelines from the American Diabetes Association (American Diabetes Association, 2010). CKD stages were defined by the estimated glomerular filtration rate (eGFR) calculated with the Modification of Diet in Renal Disease (MDRD) formula (National-Kidney-Foundation, 2002) at the time of the first assessment.

The study was approved by the local ethnics committee and written informed consent was obtained from each participant. The study was conducted according to the principles of the Declaration of Helsinki.

2.2. Blood measurements

Several laboratory parameters were collected at baseline and determined using a standard methodology in routine blood samples drawn after an overnight fast. We analyzed hemoglobin (Hb), albumin, glycosylate hemoglobin (HbA1c) and eGFR according to the MDRD formula. The urine albumin/creatinine ratio (UACR) was obtained under standardized conditions using the first voided morning midstream specimen. We also analyzed markers of mineral metabolism including intact parathormone (iPTH), phosphorus and calcium. Inflammation (interleukin 6—IL6) and lipid profile (total cholesterol, HDL, LDL, triglycerides) were also evaluated. To evaluate insulin resistance we analyzed fasting insulin and glucose.

2.3. Definitions

The degree of insulin resistance was estimated using the homeostasis model assessment insulin resistance (HOMA-IR) parameter whose utility and reliability have been validated in patients with CKD (Caravaca et al., 2010). HOMA-IR was modeled as a continuous variable or as a categorical variable (terciles). This parameter was calculated using the following formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 (American Diabetes Association, 2010; Caravaca et al., 2010).

Left ventricular mass index (LVMI) was calculated by applying the regression equation from Penn convention (Devereux & Reichek, 1977): LV mass = 1.04 [(LVIDD + PWTD + IVSTD)3 − (LVIDD)3] − 13.6 g. Where LVIDD = left ventricular internal diameter in diastole, PWTD = posterior wall thickness in diastole and IVSRD = interventricular septum thickness in diastole. LVMI was then obtained by dividing LV mass by body surface area.

Body mass index (BMI) was calculated as weight (Kg) divided by height (m^2).

Cardiovascular hospitalizations/admissions were classified on discharge, considering only admissions caused by coronary heart disease (myocardial infarction, stable or unstable angina pectoris), congestive heart failure, peripheral vascular disease and cerebrovascular disease (stroke or transient ischemic attacks) based on recent international guidelines (Kavousi, Leening, Nanchen, et al., 2014). According to the presence or absence of cardiovascular hospital admission during the study period our population was divided in two groups: G-1—with cardiovascular hospitalization ($n = 48$,) and G-2—without cardiovascular hospitalization ($n = 71$). To analyze the risk factors of ESRD we considered as the renal outcome the initiation of dialysis.

2.4. Statistical analyses

Statistical analysis was performed with SPSS 17.0 for Windows. Descriptive statistics, Student's t-test and χ^2 test were used. For comparisons between HOMA-IR terciles we used the ANOVA and the Scheffé test for post hoc analysis. To assess predictors of

Table 1
Summary demographics of the entire cohort and for each CKD stage.

Characteristics	Entire cohort ($n = 119$)	CKD stage 2 ($n = 32$)	CKD stage 3 ($n = 47$)	CKD stage 4 ($n = 40$)
Age (years)	62.7 ± 12.4	55.8 ± 12.3	66.0 ± 11.3	66.0 ± 11.1
Gender (male/female)	65/54	20/12	24/33	21/19
BMI (kg/m^2)	26.6 ± 4.9	27.2 ± 4.9	26.9 ± 4.7	25.5 ± 5.2
LVMI (g/m^2)	108.2 ± 25.5	95.6 ± 18.9	113.5 ± 24.2	136.0 ± 22.5
Albumin (g/dl)	4.2 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	4.0 ± 0.6
Hemoglobin (g/dl)	12.7 ± 1.8	13.8 ± 1.6	12.8 ± 1.4	11.6 ± 1.8
iPTH (pg/ml)	132.4 ± 10.0	73.3 ± 52.3	129.2 ± 75.1	195.2 ± 147.9
Calcium (mg/dl)	9.5 ± 0.8	9.3 ± 1.1	9.6 ± 0.7	9.6 ± 0.6
Phosphorus (mg/dl)	4.3 ± 1.1	3.7 ± 0.7	4.3 ± 1.1	4.9 ± 1.4
Total cholesterol (mg/dl)	195.3 ± 41.8	184.3 ± 39.3	198.7 ± 34.9	202.6 ± 49.6
HDL (mg/dl)	49.9 ± 19.5	50.7 ± 20.8	52.8 ± 22.0	45.8 ± 14.2
Triglycerides (mg/dl)	158.2 ± 100.9	149.0 ± 117.6	146.3 ± 62.9	181.6 ± 115.8
LDL (mg/dl)	118.3 ± 35.4	110.2 ± 32.0	120.8 ± 35.1	127.5 ± 39.9
UACR (mg/g)	245.2 ± 131.7	210.4 ± 125.6	240.1 ± 140.9	278.4 ± 122.0
Interleukin 6 (pg/ml)	5.0 ± 3.1	3.2 ± 2.3	5.3 ± 2.9	6.5 ± 3.3
Plasma glucose (mg/dl)	183 ± 66	120.0 ± 40.5	172.5 ± 55.0	255.5 ± 75.0
Insulin (μU/ml)	14.8 ± 3.2	11.7 ± 2.2	13.7 ± 3.0	16.5 ± 4.5
HOMA-IR	2.0 ± 0.5	1.1 ± 1.2	2.0 ± 1.7	2.8 ± 1.9

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